Universal definition of perioperative bleeding in adult cardiac surgery

Cornelius Dyke, MD,[a] Solomon Aronson, MD,[b] Wulf Dietrich, MD, PhD,[c] Axel Hofmann, ME,[d,e,f,g] Keyvan Karkouti, MD,[h,i] Marcel Levi, MD, PhD,[j] Gavin J. Murphy, MD, FRCS,[k] Frank W. Sellke, MD,[l] Linda Shore-Lesserson, MD,[m] Christian von Heymann, MD,[n] and Marco Ranucci, MD[o]

Objectives: Perioperative bleeding is common among patients undergoing cardiac surgery; however, the definition of perioperative bleeding is variable and lacks standardization. We propose a universal definition for perioperative bleeding (UDPB) in adult cardiac surgery in an attempt to precisely describe and quantify bleeding and to facilitate future investigation into this difficult clinical problem.

Methods: The multidisciplinary International Initiative on Haemostasis Management in Cardiac Surgery identified a common definition of perioperative bleeding as an unmet need. The functionality and usefulness of the UDPB for clinical research was then tested using a large single-center, nonselected, cardiac surgical database.

Results: A multistaged definition for perioperative bleeding was created based on easily measured clinical end points, including total blood loss from chest tubes within 12 hours, allogeneic blood products transfused, surgical reexploration including cardiac tamponade, delayed sternal closure, and the need for salvage treatment.

From the Department of Cardiothoracic Surgery,[a] University of North Dakota School of Medicine and Health Sciences, Sanford Health Fargo, Fargo, ND; Department of Anesthesiology,[b] Duke University Medical Center, Durham, NC; Institute for Research in Cardiac Anesthesia,[c] Munich, Germany; Institute of Anaesthesiology,[d] University Hospital, Zurich, Switzerland; School of Surgery,[e] Faculty of Medicine, Dentistry and Health Sciences, University of Western Australia, Perth, Western Australia; Centre for Population Health Research,[f] Curtin Health Innovation Research Institute (CHIRI), Curtin University, Perth, Western Australia; Medical Society for Blood Management,[g] Laxenburg, Austria; Department of Anesthesia,[h] Toronto General Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada; Institute of Health Policy, Management and Evaluation,[i] University of Toronto, Toronto, Ontario, Canada; Department of Vascular Medicine and Internal Medicine,[j] Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; Department of Cardiovascular Sciences,[k] University of Leicester, Clinical Sciences Wing, Glenfield General Hospital, Leicester, United Kingdom; Division of Cardiothoracic Surgery,[l] Alpert Medical School of Brown University, Rhode Island Hospital, Providence, RI; Department of Anesthesiology,[m] North Shore University Hospital and Long Island Jewish Medical Center, Hofstra University School of Medicine, Manhasset, NY; Department of Anesthesiology and Intensive Care Medicine,[n] Charité-Universitätsmedizin Berlin, Berlin, Germany; and Department of Cardiothoracic and Vascular Anesthesia and Intensive Care,[o] IRCCS Policlinico San Donato, Milan, Italy.

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Address for reprints: Cornelius Dyke, MD, Department of Cardiothoracic Surgery, University of North Dakota School of Medicine and Health Sciences, Sanford Health Fargo, Fargo, ND 58122 (E-mail: cornelius.dyke@sanfordhealth.org).

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Depending on these components, bleeding is graded as insignificant, mild, moderate, severe, or massive. When applied to an established cardiac surgery dataset, the UDPB provided insight into the incidence and outcome of bleeding after cardiac surgery.

Conclusions: The proposed UDPB in adult cardiac surgery provides a precise classification of bleeding that is useful in everyday practice as well as in clinical research. Once fully validated, the UDPB may be useful as an institutional quality measure and serve as an important end point in future cardiac surgical research. (J Thorac Cardiovasc Surg 2014;147:1458-63)

Supplemental material is available online.

Perioperative bleeding in patients undergoing cardiac surgery is common. Bleeding may be insignificant and not require treatment or may be serious and life threatening. Bleeding is frequently treated with allogeneic blood product transfusion (packed red blood cells [PRBCs], fresh frozen plasma [FFP], or platelet concentrates [PLT]). Although transfusion is recognized to adversely affect early and late outcomes,[1-4] it remains common after cardiac surgery despite improvements in transfusion medicine and system-based protocols.[5-8]

Periprocedural bleeding has become an important outcome measure in cardiology practice and frequently serves as a component of combined end points in randomized clinical trials (RCTs).[9-11] Although precise definitions for complications such as renal failure, acute myocardial infarction, and neurologic complications after cardiac surgery exist,[12-16] no standardized definition for perioperative bleeding has been established, making the interpretation of clinical trials more difficult and hindering attempts to study patient blood management. We propose that a more precise definition of perioperative bleeding based on easily measurable clinical variables would improve analysis of this clinical problem and be useful as a measure of clinical quality. A universal definition of perioperative bleeding (UDPB) in adult cardiac surgery would standardize nomenclature, improve outcome definitions, and be useful in future clinical trials. The UDPB may also serve as a measure for institutional quality improvement and a tool to propose, test, and implement solutions to reduce bleeding and transfusion.

MATERIALS AND METHODS

The authors are involved in the International Initiative for Haemostasis Management in Cardiac Surgery, an international, multidisciplinary collaboration with interest and expertise in the perioperative management of bleeding associated with cardiac surgery, patient blood management, and transfusion avoidance. The group recently published an editorial document addressing current areas in which solid data are lacking to guide blood management in adult cardiac surgery patients.[17]

The UDPB was conceived and defined through a series of face-to-face and interpersonal meetings and represents the consensus opinion of the group (Table E1). The UDPB was tested using a large, clinical, cardiac, surgical database (IRCCS Policlinico San Donato, Milan, Italy), which prospectively included all patients undergoing cardiac surgery since 2000. A retrospective analysis of patients who underwent surgery in 2011 was performed in a post hoc analysis of a recently published study[18] that was approved by the local ethics committee with a waiver of written informed consent. Data routinely included in the database were supplemented with additional data from patient files as needed. To verify the clinical impact of this stratification, operative (30-day) mortality rates were analyzed and statistically compared for between-group differences. Multivariate analyses (linear, logistic regression) were applied to assess determinants of UDPB class and the impact of this classification on operative mortality. A computerized statistical package (SPSS 13.0, Chicago, Ill) was used.

RESULTS

UDPB

The UDPB is based on 9 events occurring during surgery or within the first postoperative day: (1) delayed sternal closure, (2) postoperative chest tube output, (3) PRBC transfusion, (4) FFP transfusion, (5) PLT transfusion, (6) cryoprecipitate transfusion, (7) use of factor concentrates, (8) use of recombinant activated factor VII (rFVIIa), and (9) surgical reexploration. The UDPB defines 5 perioperative bleeding classes, which are designed to characterize the severity of bleeding, regardless of its source. The contribution of each of these events to the UDPB is presented in Table 1.

Rationale

The presence of the worst, single, predefined attribute is sufficient to place a patient in a particular bleeding class; the presence of all attributes within a class is not necessary. Chest tube output or magnitude of transfusion are not the sole criteria for the classification. This approach is conservative and ensures the capture of significant bleeding events. For example, early surgical reexploration may limit total transfusion or total chest tube output, yet our classification identifies the patient as experiencing a severe or class 3 bleeding event. We recognize that the decision to reexplore is surgeon dependent and subjective, however reexploration is associated with recognized adverse consequence,[19] and the categorization as severe attempts to reflect this. This worst-parameter principle was applied throughout the bleeding classification system.

1. Delayed sternal closure

Delayed sternal closure in clinical practice identifies patients who experience severe, refractory, intraoperative

Abbreviations and Acronyms
FFP = fresh frozen plasma
PCC = prothrombin complex concentrates
PLT = platelet concentrate
PRBC = packed red blood cells
RCT = randomized clinical trials
UDPB = universal definition for perioperative bleeding

bleeding. In the UDPB, delayed sternal closure is defined as leaving the operating room with an open or packed chest.

2. Chest tube output

Quantification of intraoperative blood loss using sponge weight is not commonly used in daily practice and therefore not included as a determinant in the UDPB. Moreover, bleeding before protamine administration is not commonly measured either in clinical practice or in RCTs.

Postoperative chest tube output is easily quantifiable, routinely used in clinical practice, and has been used as an outcome measurement in clinical trials.[20-22] Limitations exist, however; early reexploration for a high rate of chest tube output may limit total blood loss, whereas late chest tube output may represent accumulation of serum as well as blood. We propose blood loss beginning with chest closure and over the first 12 hours as a measure for the UDPB, because it reflects early perioperative events and specifically excludes intraoperative transfusion during cardiopulmonary bypass to treat preoperative anemia. We recognize that several definitions of severe bleeding based on the rate of blood loss exist,[23-26] but are variably applied. Clearly defined cut-off points are included in the UDPB, because they are easily measureable and offer a standard definition.

3, 4, and 5. Allogeneic blood product transfusion

Transfusion of allogeneic blood products is usually included in studies that address perioperative bleeding in cardiac surgery.[2,21,22,27,28] Transfusions of blood products do not directly measure bleeding in cardiac surgery and transfusion variability is widely acknowledged, however a link between severity of bleeding and magnitude of blood transfused exists. Several studies have used the number of transfusions for empirical and nonstandardized definitions for severe (major) and massive bleeding.[2,28,29]

We propose that the number of allogeneic blood products transfused according to predefined definitions should be considered for grading of bleeding severity within the UDPB. Transfusion of PRBCs in the absence of other clinical signs of bleeding is typically triggered by an anemic state potentially related to preoperative anemia or excessive hemodilution. In the UDPB, PRBC units should be considered when accompanied by other signs of perioperative bleeding and should not be considered if used preoperatively or intraoperatively to correct preexisting anemia unrelated to bleeding. Accordingly, for the purposes of the UDPB, we count transfusions beginning at chest closure to avoid preoperative or intraoperative transfusion, which may not reflect blood loss. The same applies to the use of PLT, cryoprecipitate, or FFP to correct thrombocytopenia or coagulation factor deficiencies. For instance, administration of fibrinogen concentrate to correct low preoperative fibrinogen levels would not considered in the bleeding classification.

6. The use of cryoprecipitate

The availability and use of cryoprecipitate varies between different geographic regions, but, when available, is frequently used to treat ongoing blood loss and coagulopathy by supplementing fibrinogen levels. Thus, cryoprecipitate is a relevant marker for significant bleeding in the UDPB (at least class 2 or moderate). In regions where cryoprecipitate is not available and fibrinogen concentrate is used, a similar class 2 classification would result. Preoperative administration of cryoprecipitate or fibrinogen concentrate to correct preexisting hypofibrinogenemia would not factor into the classification according to the UDPB.

7. The use of factor concentrates

The use of fibrinogen and prothrombin complex (PCC) concentrates should be considered as a marker for moderate bleeding in the UDPB when used as therapy after surgery. We recognize that prophylactic administration of PCC before surgery is practiced in patients exposed to oral antithrombotics, but the UDPB definition only includes use during or after the surgical procedure.[30] In principle, we consider factor replenishment with either blood products or concentrates as a marker for ongoing bleeding due to factor deficiency. If a coagulopathy is mitigated with the judicious use of a modest dose of factor concentrate, we define this as moderate or class 2 bleeding. If persistent bleeding continues, upstaging is ensured by the presence of other attributes in the definition, such as magnitude of PRBCs transfused, chest tube output, or reexploration (Table 1).

8. The use of rFVIIa

rFVIIa concentrate is used for difficult, refractory, and life-threatening bleeding.[31,32] The use of rFVIIa under less severe bleeding circumstances should be avoided because of the potential risk of thromboembolic complications.[33] The lack of specific criteria guiding the use of rFVIIa is a weakness of this metric; nonetheless, the use of rFVIIa has evolved to portend the treatment of massive bleeding when other treatment options have failed, and is scored accordingly.

TABLE 1. Bleeding categories according to the UDPB in adult cardiac surgery (if different categories indicate mixed definitions of bleeding, the worst definition applies)

Bleeding definition	Sternal closure delayed	Postoperative chest tube blood loss within 12 hours (mL)	PRBC (units)	FFP (units)	PLT (units)	Cryoprecipitate	PCCs	rFVIIa	Reexploration/ tamponade
Class 0 (insignificant)	No	<600	0*	0	0	No	No	No	No
Class 1 (mild)	No	601-800	1	0	0	No	No	No	No
Class 2 (moderate)	No	801-1000	2-4	2-4	Yes	Yes	Yes	No	No
Class 3 (severe)	Yes	1001-2000	5-10	5-10	N/A	N/A	N/A	No	Yes
Class 4 (massive)	N/A	>2000	>10	>10	N/A	N/A	N/A	Yes	N/A

UDPB, Universal definition for perioperative bleeding; *PRBC*, packed red blood cells; *FFP*, fresh frozen plasma; *PLT*, platelet concentrates; *PCCs*, prothrombin complex concentrates; *rFVIIa*, recombinant activated factor VII; *N/A*, not applicable. *Correction of preoperative anemia or hemodilution only; the number of PRBCs used should only be considered in the UDPB when accompanied by other signs of perioperative bleeding.

9. Surgical reexploration

Surgical reexploration is a common rescue technique when operative techniques or transfusions fail to stop ongoing blood loss, but is not innocuous and adversely affects outcomes after cardiac surgery.[19] Surgical reexploration can occur early or late, and although the temporal relation to chest tube blood loss may be variable, we consider it to always be a significant negative clinical event.[34,35] The incidence of postoperative reexploration is easily measured and frequently used as a quality indicator.[28,29,35] Surgical reexploration is included in the UDPB as a measure of severe bleeding.

A postsurgical change in hemoglobin concentration was considered, but is not a component of the UDPB. Although decrease in hemoglobin concentration is included as part of a definition of bleeding for use in nonsurgical cardiovascular trials,[9] hemoglobin changes in the cardiac surgery setting may not be directly related to bleeding. Significant decreases in hemoglobin concentration may result in transfusion, which is a component of the definition.

Using the UDPB for Database Queries: A Test Case

The UDPB was used to analyze a nonselected series of 1144 adult patients who underwent cardiac operations at a single institution during the 2011 calendar year. The type of cardiac operations performed is summarized in Table E2 and the UDPB distribution is shown in Figure 1. More than 50% of the patient population had insignificant bleeding and 10% of patients had bleeding categorized as severe and massive.

The 9 event categories were successful in adjudicating patients to the appropriate UDPB class, and adjudication to the UDPB classes was conservative, so that a single attribute was sufficient to upgrade a patient's bleeding classification. Patients were attributed to class 1 or mild bleeding (n = 170) largely as a result of the number of PRBC units transfused (n = 97, 57%) and the amount of postoperative chest drain blood loss (n = 66, 39%), Patients with class 2 or moderate bleeding (n = 274) were principally assigned as a result of the number of PRBC units transfused (n = 151, 55%), followed by a combination of different events (n = 67, 24%), platelet concentrate use (n = 22, 8%), chest drain blood loss (n = 12, 4.4%), FFP use (n = 11, 4%), and delayed sternal closure (n = 10, 4%). Patients in the severe bleeding class (n = 94) were adjudicated based on the number of PRBC units administered (n = 49, 52%), followed by a combination of events (n = 24, 25%), chest drain blood loss (n = 15, 16%), surgical revision (n = 4, 4%), and FFP use (n = 2, 2%). Patients who experienced massive bleeding (n = 18) were adjudicated based on a combination of events (n = 10, 56%), PRBC transfusion (n = 5, 28%), and administration of rFVIIa as salvage therapy (n = 3, 17%).

The determinants of UDPB class were explored with univariate and multivariate analyses. Factors considered were the preoperative risk stratification (logistic EuroSCORE I), plus additional variables not included in the EuroSCORE (diabetes, preoperative use of low-molecular-weight heparin, type of operation, preoperative hematocrit, and cardiopulmonary bypass duration). Independent predictors of the UDPB class were EuroSCORE, preoperative hematocrit, and cardiopulmonary bypass duration (Table 2). Because

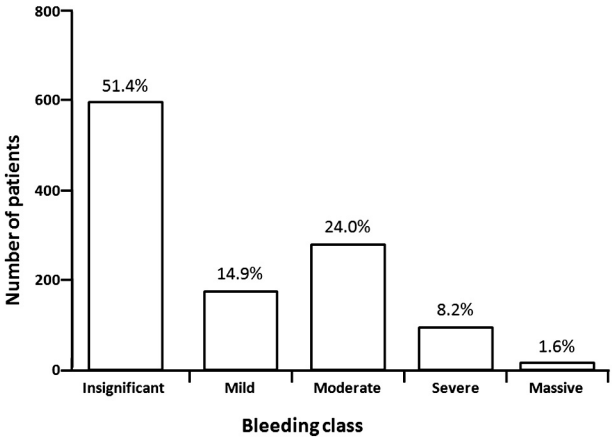

FIGURE 1. Bleeding classification according to the UDPB using a test series (N = 1144).

TABLE 2. Independent predictors of UDPB classification

UDPB class	n	EuroSCORE score (%)	Preoperative hematocrit (%)	CPB duration, minutes (SD)
Class 0 (insignificant)	588	4.7 (5.2)	40.0 (4.3)	78.2 (30.6)
Class 1 (mild)	170	5.5 (4.8)	38.2 (3.9)	77.2 (29.1)
Class 2 (moderate)	274	11.1 (12.3)	35.5 (5.1)	99.1 (47.8)
Class 3-4 (severe-massive)	112	13.0 (15.4)	35.5 (6.5)	138.5 (81.4)
P value		.001	.001	.001

UDPB, Universal definition for perioperative bleeding; *CPB*, cardiopulmonary bypass; *SD*, standard deviation.

of the low number of patients in UDPB class 4 (18 patients), for the purposes of this analysis, UDPB classes 3 (severe) and 4 (massive) were merged into a single class.

UDPB and Operative Mortality

In a further analysis, the operative (30-day) mortality rate in each of the UDPB classes was explored. Higher classification within the UDPB correlated with higher mortality in the univariate analysis. There were significant differences between bleeding classes, with a low mortality rate in patients classified as having irrelevant or mild bleeding, and significantly higher values in patients experiencing moderate, severe, or massive bleeding. Patients with severe or massive bleeding had a combined mortality of 22.3%.

These data were adjusted for the potential confounders previously identified (EuroSCORE, preoperative hematocrit, and cardiopulmonary bypass duration) in a multivariate logistic regression model. Within this model, the UDPB class remained an independent predictor of operative mortality, with an odds ratio of 2.18 (95% confidence interval, 1.55-3.07; $P = .001$), corresponding to a relative risk of operative mortality that doubles with each increase in UDPB class. Crude and adjusted mortality rates are shown in Figure 2.

DISCUSSION

Excessive bleeding after cardiac surgery remains a complex clinical problem despite significant advances in surgical technique, anesthetic management, and critical care. Although there is general agreement that less bleeding is better and avoidance of transfusion a laudatory goal, all patients bleed after surgery and it remains unclear at what point bleeding becomes clinically significant. We believe that these questions can only be tested with a more precise definition of bleeding. The UDPB uses multiple clinically relevant parameters to create a simple 5-class system that can be applied in everyday practice and in clinical investigations to classify perioperative bleeding.

Limitations and some arbitrariness exist with any definition of bleeding. Chest tube output is a continuous measurement of flow, and we acknowledge that the difference between 750 and 800 mL of chest tube drainage is probably irrelevant. This is mitigated by the use of multiple criteria in addition to chest tube output in the UDPB. The UDPB is intended to quantify and define perioperative bleeding, not transfusion for other reasons or outside the perioperative period. The UDPB is also not meant to be predictive or identify risk factors for bleeding, but to define bleeding when it occurs. It is to be hoped that this definition will serve as a tool for future investigations and modifications can be expected based on clinical evidence.

Our test case suggests that the UDPB is useful as a descriptive tool and may assist in predicting clinical outcomes. Different classes of bleeding were associated with different mortality rates after adjustment for the other relevant confounders. Two thirds of postsurgical bleeding was insignificant or mild, and mortality among these patients was low. No differences in mortality were seen between the insignificant or mild bleeding classes. Moderate bleeding, however, was associated with a significant increase in mortality, and mortality rates continued to increase dramatically for severe and massive bleeding. Although the high mortality associated with severe or massive bleeding confirms clinical experience, in the test case, mild bleeding was truly insignificant, which suggests that efforts to shift patients from moderate bleeding to an insignificant or mild bleeding category seem worthwhile. Other clinical outcomes such as length of stay in the intensive care unit or ventilation await future analysis.

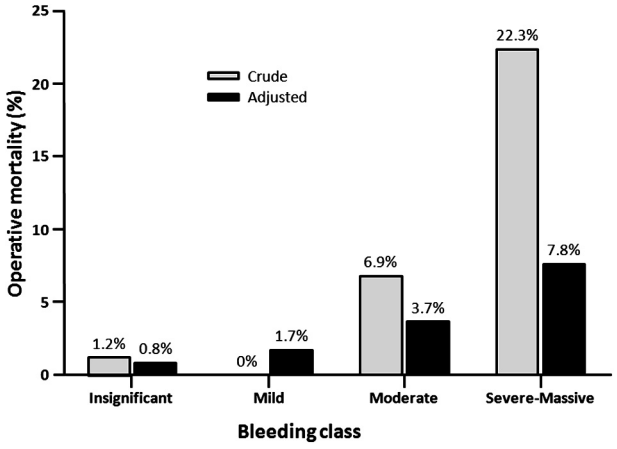

FIGURE 2. Mortality according to the UDPB classification scheme using a test series (N = 1144).

CONCLUSIONS

Postoperative bleeding in most cardiac surgical patients does not require transfusion, does not adversely affect hospital course, and is without clinical consequence. Despite algorithms to identify patients at high risk for bleeding and consensus guidelines for the prevention of postoperative bleeding, the definition of bleeding in the cardiac surgical patient is variable. The UDPB precisely defines the magnitude of perioperative bleeding, and preliminary investigation suggests that these classes have clinical relevance and may correlate with postoperative mortality. We propose that the UDPB may be helpful in defining strategies and improving implementation of demonstrated protocols to minimize bleeding and transfusion in cardiac surgical patients.

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TABLE E1. Literature search strategies

Search	Topic, subtopic, and MeSH terms	Date	No. of hits
1	Blood loss during cardiac surgery (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh])	December 5, 2011	865
2	Treatment Outcome (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Treatment Outcome”[Mesh]	December 5, 2011	278
3	Blood Transfusion (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Blood Transfusion”[Mesh]	December 5, 2011	286
4	Erythrocyte Transfusion (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Erythrocyte Transfusion”[Mesh]	December 5, 2011	51
5	Plasma (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Plasma”[Mesh]	December 5, 2011	17
6	Platelet Transfusion (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Platelet Transfusion”[Mesh]	December 5, 2011	17
7	Factor VIIa (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Factor VIIa”[Mesh]	December 5, 2011	51
8	Reoperation (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Reoperation”[Mesh]	December 5, 2011	159
9	Cardiac Tamponade (“Cardiac Surgical Procedures”[Mesh] OR “Coronary Artery Bypass”[Mesh] OR “Cardiopulmonary Bypass”[Mesh] OR “Extracorporeal Circulation”[Mesh]) AND (“Postoperative Hemorrhage”[Mesh] OR “Blood Loss, Surgical”[Mesh] OR “Hemostasis, Surgical”[Mesh]) AND “Cardiac Tamponade”[Mesh]	December 5, 2011	16

Comprehensive literature searches were performed using the indexed online database MEDLINE/PubMed. Lists of cited literature within relevant articles and the authors’ own libraries were also screened. Boolean operators and Medical Subject Heading (MeSH) thesaurus keywords were applied as a standardized use of language to unify differences in terminology into single concepts. Searches were limited to human studies, adults, and published in the last 10 years. Full publications were retrieved based on evaluation of abstracts that were deemed relevant to the queries posed.

TABLE E2. Type of surgical operation performed in the single-center patient test series

Operation	n (%)
Isolated coronary revascularization	347 (30)
Isolated mitral valve procedure	191 (17)
Isolated aortic valve procedure	188 (16)
Coronary revascularization + valve procedure	180 (16)
Coronary revascularization + left ventricle aneurismectomy	39 (3)
Double/triple valve	114 (10)
Ascending aorta/aortic arch procedure	85 (7)
Total	1144 (100)